REMARKS/ARGUMENTS

The Pending Claims

Upon entry of this amendment, claims 1, 3, 4, 13, and 30-36 will be pending and are directed to a method for the therapeutic treatment of a carcinoma in a mammal.

The Amendments to the Claims

Claim 1 has been amended to delete reference to a low molecular weight substance. Claims 30-32 are new and are the same as pending claims 3 and 13 except for different dependencies. Claim 33 is new and is similar to claim 1 except for specifying the use of an anti-FGFR-4 antibody (as compared to an anti-FGFR-4 antibody and/or a kinase inactive FGFR-4). Claims 34-36 are new and are the same as pending claims 3 and 13 except for being directly or indirectly dependent on claim 33. Claims 30-36 are supported by the claims as originally filed, and by the specification at, e.g., page 4, lines 20-22. Accordingly, no new matter has been added by way of these amendments.

The Office Action

The Office Action rejects claims 1 and 3 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claims 1, 3, 4, and 13 are rejected under 35 U.S.C. § 103 as allegedly obvious over Johnston et al., *Biochem. J.*, *306*: 609-616 (1995) ("the Johnston reference"). Reconsideration of these rejections is hereby requested.

Discussion of Written Description Rejection

The Office Action has rejected claims 1, 3, 4, and 13 under Section 112, first paragraph, as allegedly lacking written description. This rejection is traversed for the reasons set forth below.

The Office Action alleges that, while the specification adequately discloses certain inhibitors of mutated FGFR-4 (i.e., kinase-inactive FGFR-4 and antibodies directed against the FGFR-4 receptor), the specification does not adequately disclose low molecular weight inhibitors of FGFR-4. While Applicants disagree with the rejection, claim 1 has been amended to delete reference to low molecular weight inhibitors of FGFR-4. Accordingly, the

subject matter of claim 1, as well as the claims depending therefrom, is adequately described in the specification. Thus, the written description under Section 112, first paragraph, should be withdrawn.

Discussion of Obviousness Rejection

Claims 1, 3, 4, and 13 are rejected under Section 103 as allegedly obvious over the Johnston reference. This rejection is traversed for the reasons set forth below.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited reference.

Regarding the scope and content of the prior art, the Johnston reference discloses the effects of aFGF and bFGF on breast cell lines (normal and cancerous). Specifically, the Johnston reference demonstrates that aFGF and bFGF induce membrane ruffling of some breast cancer cell lines, which is associated with directional cell migration. Membrane ruffling was inhibited by dominant-negative mutants of the FGF receptor 3 (FGFR-3). The Johnston reference further discloses that FGFR-4 can mediate membrane ruffling in Cos-7 cells.

For the sake of argument and for purposes of the present analysis, one of ordinary skill in the art can be assumed to be someone with an advanced degree and a few years of experience in the relevant art.

With regard to the differences between the claimed invention and the prior art, the Johnston reference does not disclose or suggest a method for treating a carcinoma in a mammal wherein (i) the mammal comprises a mutated fibroblast growth factor receptor-4 (FGFR-4) protein, and (ii) the mutated FGFR-4 protein comprises the amino acid sequence of SEQ ID NO: 9 except that glycine at position 388 of SEQ ID NO: 9 has been substituted with arginine, which method comprises administering to the mammal an effective amount of at least one inhibitor of the mutated FGFR-4 selected from the group consisting of an anti-FGFR-4 antibody and a kinase inactive FGFR-4.

In this respect, the membrane ruffling assay disclosed in the Johnston reference was not an established model of tumorigenesis or metastasis at the time the present application was filed. Indeed, the Johnston reference confirms that the potential role of membrane ruffling in cancer cell metastasis is unclear by stating that "[m]embrane ruffling is associated with cell motility and therefore *could be important* in determining the metastatic potential of cells" (see Johnston reference at page 614, second column, ¶1, emphasis added). In addition, the Johnston reference does not provide any evidence that FGFR-4 is involved in cancer or metastasis. In this respect, the Johnston reference discloses a *possible* role for FGFR-4 in membrane ruffling of *non-cancer* cells (i.e., Cos-7 cells), and speculates that FGFR-4 "may have a role in breast tumorigenesis" (see Johnston reference at page 608, second column, lines 3-4). The Cos-7 cell line is derived from normal hamster ovary tissue, and the Johnston reference discloses that aFGF/bFGF cannot induce membrane ruffling of normal breast cells. Thus, the Cos-7 experiments disclosed in the Johnston reference represent, at most, an artificial *in vitro* system that is not predictive of the *in vivo* situation in cancer patients.

In view of the foregoing, the Johnston reference cannot be interpreted as reasonable suggesting to one of ordinary skill in the art that FGFR-4 is a target for for cancer-inducing mutations, much less that FGFR-4 inhibitors would be useful to treat cancer. As such, one of ordinary skill in the art would not have been motivated to modify the disclosure of the Johnston reference in the manner alleged in the Office Action and arrive at the subject matter of the pending claims with a reasonable expectation of success.

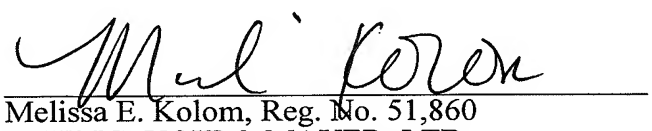
Considering all of the Graham factors together, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of

the combination of cited references. Accordingly, the obviousness rejections under Section 103 should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



Melissa E. Kolom, Reg. No. 51,860
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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